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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/737,457	03/12/97	CARDY	D	960670.ORI

HM22/0103

ORRIN M HAUGEN
HAUGEN AND NIKOLAI
820 INTERNATIONAL CENTRE
900 SECOND AVENUE SOUTH
MINNEAPOLIS MN 55402-3325

EXAMINER	
EWOLDT,G	
ART UNIT	**PAPER NUMBER**
1644	17

DATE MAILED: 01/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/737,457	Cardy et al.17
Examiner	**Group Art Unit**
Gerald Ewoldt	1644

☐ Responsive to communication(s) filed on 8/12/99 and 10/13/99 .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3 and 5-24* is/are pending in the application.

Of the above, claim(s) *24* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1-3 and 5-23 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

~~A~~ Notice to comply with Sequence Rule.

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

1. The request filed on 10/13/99 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/737,457 is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicant's Amendment, filed 8/12/99 (Paper No. 13), and Preliminary Amendment, filed 10/13/99 (Paper No. 16), are acknowledged.

3. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Gerald R. Ewoldt, Group Art Unit 1644.

4. Claims 1-3 and 5-24 are pending.

5. A species election was required under 35 U.S.C. § 121 in the parent application as set forth in the Office Action of 8/4/98 (Paper No. 8) of one of **each** from the following groups:

I. A specific binding portion with binding affinity for a particular target cell component.
II. A specific effector portion.
III. A specific translocation portion.

Applicant elected an anti MHC II binding portion, a p53 effector portion, and an HIV tat translocation portion with traverse. This restriction requirement is hereby reiterated.

6. Claim 24 stands withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No.16.

Claims 1-3 and 5-23 are being acted upon.

The claimed invention being acted upon is a chimeric polypeptide comprising an anti MHC II binding portion, a p53 effector portion, and an HIV tat translocation portion. Note that a "signal" and "translocation" portion are considered the same. Also note that the search has been extended to include an MHC Class I binding portion.

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically, note the uncompliant nucleotide sequences of page 10 (last line) through page 11 (lines 2 and 5) and the peptide sequences on pages 11-13 of the specification.

8. The disclosure is objected to because of the following informalities: The sequences on pages 10 -11 must each be followed by the appropriate SEQ ID NO:, i.e. SEQ ID NO:1, SEQ ID NO:2, etc.

9. The disclosure is objected to because of the following informalities: The word "clsass", disclosed on page 2, line 27 of the specification is misspelled.
Appropriate correction is required.

10. Claim 6 objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim cannot be dependent on "any one of the preceding claims". See M.P.E.P. § 608.01(n).

11. In view of the amendments filed 8/12/99 and 10/13/99, all previous rejections have been withdrawn.

12. The following are New Grounds of Rejection.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

15. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed in claim 21 without an undue amount of experimentation. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the broad concept of "modulating the immune response" encompassed by the claim. Applicant discloses that the invention can be used for the treatment of diseases as widely varied as cancer and autoimmune disorders (page 4, second paragraph). The specification, however, fails to provide sufficient guidance regarding the specific embodiments of the invention to be used for the treatment of specific disorders. Applicant provides just two example of experiments actually performed, both of which provide only *in vitro* ^{51}Cr assay data using transformed cell lines with little relevance to *in vivo* modulation of the immune system. As noted by Derner (1994), "The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic studies in the human body." (Page 320, first column, second paragraph. Kahan states that "no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy," (page 558, column 2, first paragraph). It is therefore well established in the art that the actual

manipulation or modulation of *in vivo* immune responses is complex, unpredictable, and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1, 5-11, 13, and 20-23 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,283,323 (newly cited).

The '323 patent teaches a chimeric polypeptide comprising an immunoglobulin molecule, which itself comprises a binding portion and a translocation portion, and an effector portion. The '323 polypeptide binds a cell surface antigen (an immunoglobulin), induces internalization, and allows the immunogenic peptide to be presented by both MHC Class I and II molecules on the target cell surface so as to modulate immune responses, including CTL and T helper cell responses. The '323 polypeptide is broken down into a number of different peptides which are presented by a number of different MHC haplotypes, depending on the ability of the specific MHC molecule to bind the specific peptides.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1-3, and 5-23, are rejected under 35 U. S. C. § 103(a) as being unpatentable over U.S. Patent No. 5,283,323 in view of Fawell et al. (1994, of record), and Baier et al. (1995, newly cited), and Noguchi et al. (1994, of record).

20. The '323 patent has discussed, supra. It differs from the claimed invention in that it does not teach the use of a specific translocation portion nor does it teach the specific combination of an HIV tat translocation portion, an anti MHC binding portion, and a p53 effector portion.

21. Fawell et al. teach the use of the HIV tat protein for cellular translocation (see particularly page 668, second paragraph). They teach that HIV tat can be used as a "generic" translocation signal to deliver a diverse number of proteins intracellularly.

Baier et al. teach the use of anti MHC II antibodies for cellular targeting (see particularly page 2363-2364, **Concluding remarks**).

Noguchi et al. teach the use of p53 as an "obvious candidate for T cell recognition" because the gene is "frequently mutated in tumors of experimental animals and humans" (see particularly page 3171, first column, second paragraph and pages 3173-3174, **Discussion**).

22. From the teachings of the references it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the '323 antibody by the addition of an HIV tat translocation domain, as taught by Fawell et al., to a chimeric polypeptide (antibody) generated against MHC II, as taught by Baier et al., and combine it with a p53 effector portion, as taught by Noguchi et al. One of ordinary skill in the art would have been motivated to refine the internal cellular targeting of the chimeric antibodies of the '323 patent and target them to various cell types and combine them with various effectors as envisioned in the '323 patent. From the teachings of the established techniques there would have been a reasonable expectation of success in producing the claimed invention.

23. Applicant argues, in amendments filed 8/12/99 and 10/13/99, that the examiner has used too many references that provide too little motivation and in addition that the examiner "has impermissibly used hindsight" in making the previous rejections. Applicant argues that the examiner has not provided "any clear reason for adding the contribution of each of the references to the whole". Therefore, the number of references used in the new rejections has been halved. A new primary reference has been cited for the 35 U.S.C. § 103(a) rejections that clearly provides the sufficient motivation to make the claimed invention that the Applicant found lacking in the previous rejections. The supporting references now need supply only the specific embodiments claimed by the Applicant.

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Friday from 8:00 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Gerald Ewoldt, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
December 28, 1999

Christina Chan
CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP 1800 1640

Application No.: 08/737,457

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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